July, 2001

Responses to Comments on Vinyl Chloride by the American Chemistry Council

Comment 1: On April 6, 2001, the Health Committee submitted a detailed comment on the Chemical Toxicity Summary for vinyl chloride provided with the March 2001 version of the draft Prioritization document. OEHHA' s response to this comment recognized that there were serious deficiencies in the background document for vinyl chloride. We note that the revised Chemical Toxicity Summary has been improved by eliminating the discussion of unit risk estimates (potency factors). In other contexts, we urge OEHHA to continue to address the disparities between its unit risk estimate for vinyl chloride and the more recent estimates provided by the U.S. Environmental Protection Agency in the Toxicological Review now posted on its Integrated Risk Information System (IRIS). These inconsistencies are due both to the use of an inappropriate cancer bioassay (Drew et al.) for derivation of the cancer slope factor, and to OEHHA' s reliance on default factors that less accurately predict target tissue exposure than newer methodologies, such as the physiologically-based pharmacokinetic (PB-PK) modeling that EPA relied upon. In the April 6 submission, the Health Committee also pointed out that the earlier background document failed to address the major epidemiology studies of vinyl chloride workers that have been updated over the past ten years. OEHHA recognized that it inadvertently had omitted discussion of these studies and indicated that the draft document would be revised to include the later studies and that "[t]he later studies will be evaluated together with the older ones to arrive at a more balanced summary of all the results. The revised Chemical Toxicity Summary, however, continues to state, relying on the older studies, that "[f]ive of eight studies that examined the association of brain cancer with vinyl chloride exposure found a statistically-significant positive association between brain cancer and vinyl chloride exposure. As indicated in our comment, when the updates of these studies are considered, as was done by EPA in its recent Toxicological Review, it becomes clear that the epidemiological evidence is not sufficient justifiably to conclude that there is an association between vinyl chloride exposure and brain cancer. This has been the judgment of several independent reviewers, including Sir Richard Doll and Aaron Blair of the National Cancer Institute, as noted in our earlier comment. We urge OEHHA to move forward with the promised evaluation "to arrive at a more balanced summary of all the results" when it revises the current draft Chemical Toxicity Summary for vinyl chloride.

Finally, OEHHA recognized the importance of including the reproductive and developmental toxicity study sponsored by the Health Committee in its review, and this remains to be done.

Response 1: The purpose of the Chemical Toxicity Summary for Vinyl Chloride was to set forth the evidence that vinyl chloride may pose a differential risk to children. The main evidence for this is the animal data, which show that exposure to animals early in life results in a greater carcinogenic effect than exposure spread out over the lifetime of the animals. Human epidemiological data was briefly summarized to show that it is also

well established that vinyl chloride is a known human carcinogen. The evidence relating specifically to brain cancer has been reviewed and discussed in previous OEHHA documents, including the Public Health Goal for Drinking Water document dated September 2000 available on the OEHHA website. The epidemiological data for occupational exposures to vinyl chloride are summarized in Table 14 of that document and discussed in the accompanying text. New epidemiological studies and new evaluations of those studies may continue to appear in the future. OEHHA will need to consider all available data and interpretations before considering any actions with regard to vinyl chloride. We realize that in the response to the first public comment period we indicated we would expand our table describing the epidemiology studies and add in newer studies. In the final analysis, the epidemiological data do not provide any useful information to address the question of differential sensitivity between young and mature humans, and thus we eliminated the table. The reader is now referred to the Public Health Goal document for more information on the epidemiology studies.

OEHHA has reviewed the reproductive and developmental toxicity study referred to in the comment, and will consider it together with other related studies in its future consideration of vinyl chloride. These studies were conducted by Huntingdon Life Sciences for the Chemical Manufacturers Association. In both studies rats were exposed to vinyl chloride in air at 0, 10, 100 and 1100 ppm. No adverse reproductive effects were observed. Therefore the reproductive study authors conclude that the NOEL for reproductive effects is greater than 1100 ppm. In the developmental study an increase in kidney weight was observed in the dams exposed to 10 ppm vinyl chloride. No developmental effects were observed in the offspring at any exposure level. The study concluded that the NOEL for maternal toxicity was 10 ppm, and for developmental toxicity the NOEL was 1100 ppm. As these are negative results they are not likely to play a major part in the evaluation of differential toxicity of vinyl chloride to infants and children, but they should be considered together with other studies in future evaluations of vinyl chloride toxicity.

Comment 2: The revised Chemical Toxicity Summary for vinyl chloride provides a more complete discussion of the data supporting OEHHA' s position that infants and children may be more sensitive to the carcinogenic effects of vinyl chloride than are adults. The Health Committee continues to believe that any differential carcinogenic effect on children from vinyl chloride is highly uncertain. As noted in our earlier comment, many chemicals require microsomal P-450 enzyme formation for metabolic activation. If these enzymes are not fully developed in infants and children, they will be less susceptible to toxic effects of chemicals that require such activation, not more so. Moreover, as discussed in more detail in our earlier comment, strict federal and state regulation has reduced greatly the possibility that children will ever be exposed to vinyl chloride. As OEHHA recognizes, vinyl chloride has not been detected in the ambient air in California at or above the detection limit, except for measurements taken adjacent to vinyl chloride-related industries and landfills.

Response: OEHHA agrees that **if** the microsomal P-450 enzymes that are required for metabolic activation of vinyl chloride were not fully developed in infants and children, and if detoxification pathways remained unchanged, one might expect infants and children to be less sensitive to vinyl chloride than adults. However, the animal experiments cited in the Chemical Toxicity Summary demonstrate that young animals are more sensitive than adults to the carcinogenic effects of vinyl chloride. The final carcinogenic effect depends on both toxicokinetic factors (e.g. activation and deactivation of toxic metabolites), and toxicodynamic factors. We do not know at present which of these factors are responsible for the increased sensitivity of young animals.

OEHHA has repeatedly acknowledged that vinyl chloride is not a general ambient air exposure problem.